Meconium Ileus

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Clin Colon Rectal Surg 2018;31:121–126.

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Abstract

Cystic fibrosis is one of the most common inheritable traits in Caucasians. Meconium ileus and its potential complications are the most likely reasons that these patients will need surgical care. Surgical intervention is usually needed in the neonatal period but may also be required later in life. This article discusses the various ways cystic fibrosis can affect the gastrointestinal tract. Both the operative and nonoperative management of complicated and uncomplicated meconium ileus are discussed in the neonatal period as well as long-term issues, such as distal intestinal obstructive syndrome, fibrosing colonopathy, and rectal prolapse, all of which may be seen in older children and adults.

Keywords

- meconium ileus
- cystic fibrosis
- cystic fibrosis transmembrane conductance regulator
- distal intestinal obstruction syndrome
- epithelial sodium channels
- fibrosing colonopathy
- rectal prolapse
- newborn intestinal obstruction

Cystic fibrosis is one of the most common inheritable diseases among Caucasians with an incidence of 1 in 2,500 live births.[1,2] Incidence varies according to race with 93% of cases in the United States occurring among Whites, while only 3.6 and 0.4% cases occur in Blacks and Asian Americans, respectively.[3] In the state of California, the overall birth prevalence has been estimated at 19.9 per 100,000 births with 38.8 per 100,000 births for Whites, 37.2 per 100,000 births for Native Americans, and 17.1 per 100,000 births for Blacks.[4] Median age of survival for patients with cystic fibrosis has been estimated to be 50 years.[5] There does not appear to be a difference in mortality by gender.[6]

The pathophysiology of cystic fibrosis is based on an autosomal recessive defect in the gene on the long arm of Chromosome 7. This gene codes for the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel on epithelial surfaces. Defects in this receptor cause decreased chloride secretion and increased sodium resorption. Thousands of mutations of the CFTR gene have been identified, but the most common is known as delta F508.[7–9] The CFTR regulates epithelial sodium channels known as ENaCs, so the defect in CFTR results in unregulated ENaCs and increased sodium resorption. In both the pulmonary and gastrointestinal systems, increased sodium resorption is accompanied by water resorption resulting in dehydrated mucus in the lungs and luminal contents of the small bowel.[2] Meconium ileus is characterized by intestinal obstruction from the impaction of thickened, protein-rich, meconium inspissated in the distal ileum, possibly related to a deficiency in pancreatic enzymes and abnormal mucin production.[10]

Presentation and Diagnosis

Meconium ileus is estimated to occur in 15% of infants with cystic fibrosis and is classified as either uncomplicated or complicated.[11,12] Uncomplicated meconium ileus is characterized by a distended abdomen often noted at birth and is caused

Issue Theme Pediatric and Congenital Colorectal Diseases in the Adult Patient; Guest Editor: David M. Gourlay, MD, FACS, FAAP

DOI https://doi.org/10.1055/s-0037-1609027.
ISSN 1531-0043.

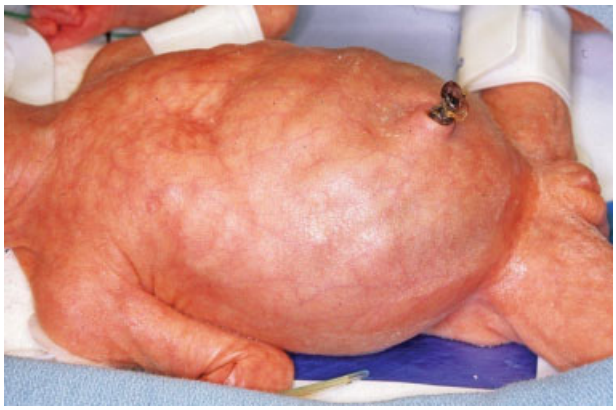

Fig. 1 Meconium ileus. Newborn with dilated loops of small bowel and a "doughy" abdomen.

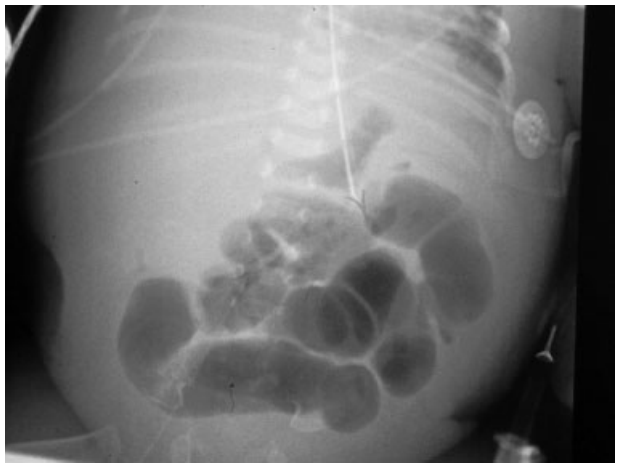

Fig. 3 Abdominal X-ray (AXR) ground glass.

by inspissated meconium in the distal ileum. This is one of the only two causes of neonatal intestinal obstruction that may manifest immediately at birth prior to infant ingestion of air (►**Fig. 1**). The other possible etiology for such obstruction is in-utero perforation with meconium cyst, which may or may not be caused by meconium ileus. Additional features of the presentation of simple meconium ileus include bilious emesis and the failure to pass meconium. Complicated meconium ileus consists of neonatal bowel obstruction with evidence of necrosis or perforation, and may include intra-abdominal calcification, erythema of the abdominal wall, and abdominal tenderness.

Diagnosis for meconium ileus includes history and physical exam as well as imaging. An abdominal radiograph will have a similar appearance in the supine and erect position without air–fluid levels despite the obstructive process. Radiographs may also demonstrate multiple loops of bowel of various sizes and a ground glass appearance (►**Figs. 2** and **3**). An ultrasound may assist in diagnosis, both pre- and postnatally. Prenatal ultrasound findings include hyperechoic masses, signifying inspissated stool.[13] There may be pseudo-thickening of the bowel wall as a result of thick and adhesive meconium. The bowel mucosa appears hyperechoic, as the desiccated meconium has a stratified appearance. Gas within the meconium becomes trapped, preventing formation of air–fluid levels.[14,15] Further characterization may proceed with a contrast enema demonstrating microcolon. Inspissated pellets along the wall of the large intestine are also typical.[16] The definitive diagnosis of cystic fibrosis is established by the presence of phenotypic or clinical characteristics of the disease in combination with genetic or biochemical alterations of the CFTR. The current gold standard is to perform biochemical analysis with the sweat chloride test, which is diagnostic at a concentration of greater than 60 mmol/L. Determination of the associated mutation of the CFTR may be useful for prognosis and to guide treatment.[9] Over 90% of patients with cystic fibrosis will have one of the 40 most common mutations that can be assessed with a discrete set of mutation probes.[11] This method, while less sensitive than an expanded gene analysis, is less likely to reveal polymorphisms and mutations of unknown significance.[11]

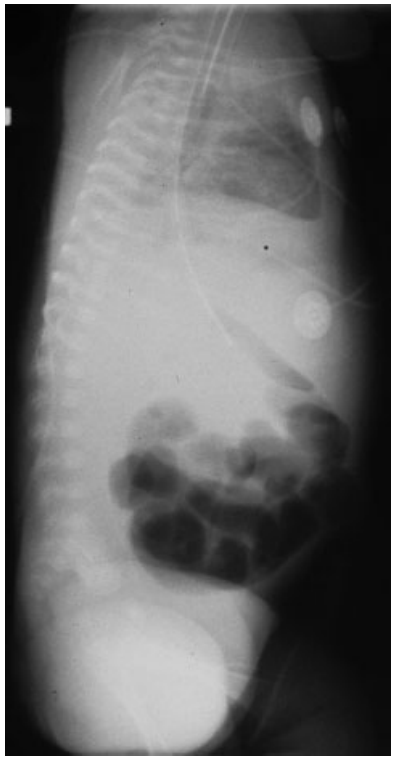

Fig. 2 Lack of air–fluid levels.

Long-term Outcomes

Several retrospective cohort studies have examined the association between initial presentation with meconium ileus and later morbidity and mortality. Four retrospective cohort studies that compared pulmonary function and nutritional status for patients diagnosed with cystic fibrosis with meconium ileus versus controls that were diagnosed as a result of other symptoms found no long-term differences between the groups.[17–20] Two earlier studies compared children presenting with meconium ileus with those diagnosed with screening for cystic fibrosis. Both of these studies found diminished pulmonary function and shorter survival for patients with meconium ileus compared with those diagnosed with prenatal screening.[21,22] It is possible that studies comparing patients presenting with meconium ileus and those diagnosed later with symptomatic disease found

no difference in long-term outcomes because those with meconium ileus may have more severe disease but benefit from early diagnosis, while those diagnosed later have the disadvantage of delayed diagnosis but the benefit of less severe disease. The study by Lai et al found that those patients with meconium ileus and those diagnosed later with symptomatic disease both had significantly shorter survival than those diagnosed with prenatal or neonatal screening.[22] Alternatively, those patients whose disease was detected with screening may have been biased by less severe phenotypes. Additionally, it appears that the differences may equilibrate with long-term analysis.

Medical/Surgical Management

Nonoperative Management

Management of meconium ileus consists of nonoperative management and surgical management of simple and complex disease. Nonoperative management consists of a hypertonic enema such as Gastrografin or other contrast enema performed under fluoroscopic guidance. Gastrografin is a hyperosmolar (1900 mOsm/L), water-soluble, radiopaque solution that contains 0.1% polysorbate 80 and 37% organically bound iodine.[13,14] Prior to initiation of contrast, the patient must undergo fluid resuscitation because the hypertonicity of the enema can lead to significant fluid shifts and cardiovascular collapse in the neonate. It may be acceptable to attempt more than one enema if progress, defined as the passing of contrast more proximally with each enema, is noted on each study. Contrast must be noted passing into the dilated loops of bowel to differentiate meconium ileus from intestinal or colonic atresia. The enema is considered failed if the meconium cannot be evacuated or contrast does not enter the dilated bowel. If a contrast enema is unsuccessful, operative intervention must follow.[13,14]

Simple Meconium Ileus

Simple meconium ileus is defined as the failure to pass meconium within 48 hours of birth without additional complications.[23] Typical management includes an attempted contrast enema and if unsuccessful, celiotomy. Historically, meconium ileus was often treated with an ostomy and postoperative irrigations to break up and evacuate the inspissated meconium. In some cases, these various types of ostomies may still be appropriate. Options for creation of an ostomy include the Bishop-Koop, a distal stoma with a proximal end-to-side anastomosis; Santulli enterostomy, a proximal stoma with a side-to-end distal anastomosis; or Mikulicz, double barrel enterostomy[13] (►**Fig. 4**). Current trends in operative management include enterotomy for irrigation with saline or N-acetylcystine. Irrigation may be completed either intraoperatively via the appendix or an enterotomy, or postoperatively through one of the ostomies mentioned previously. Use of a T-tube placed within the intestinal lumen has also been described for postoperative irrigations.[24,25] The T-tube may be removed once the meconium has cleared with spontaneous closure of the fistula.[26] Alternatively, an appendicostomy may be created for

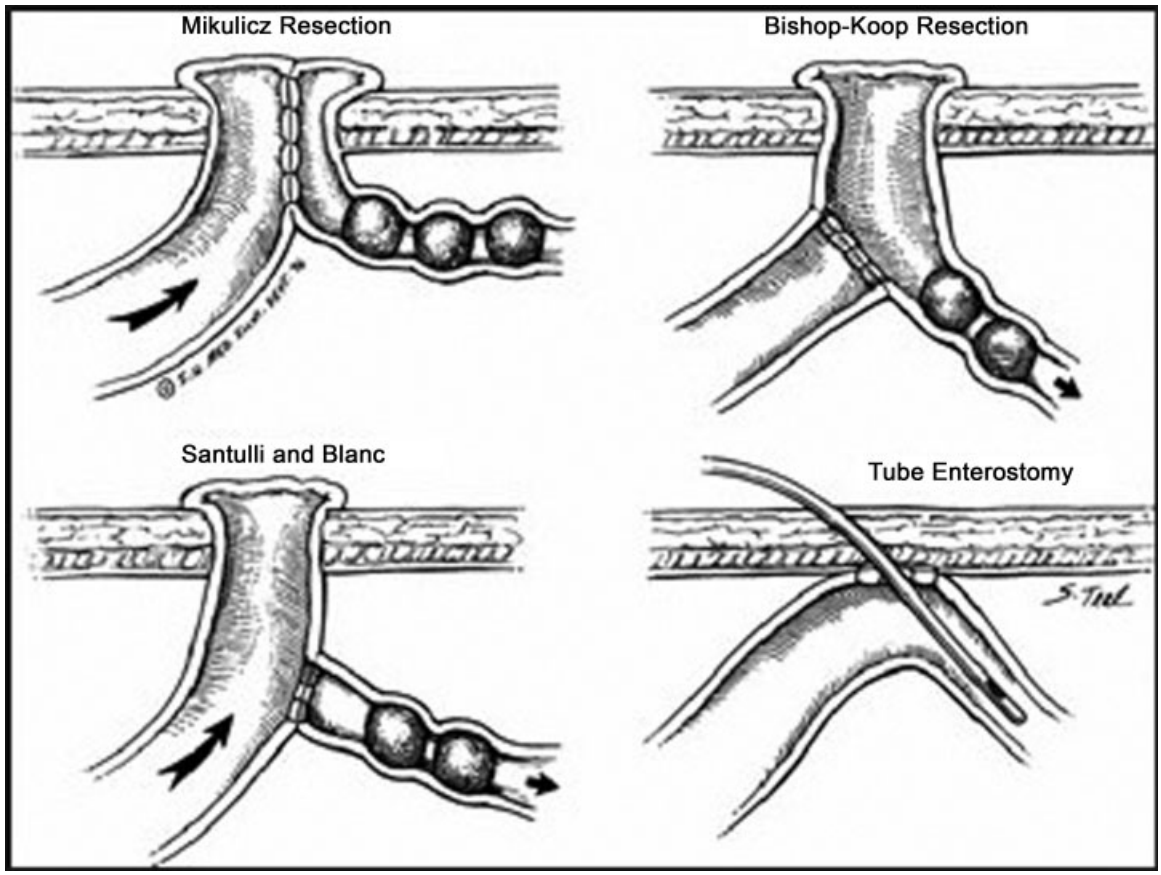

Fig. 4 Types of ostomies for meconium ileus.

ongoing irrigations.[27] In some cases, a limited bowel resection with primary anastomosis may be necessary after the inspissated meconium has been evacuated.

Complicated Meconium Ileus

Complicated meconium ileus is characterized by the addition of atresia, volvulus, and perforation, which may result in meconium cyst with peritonitis or gangrene.[28] An ultrasound may demonstrate free intraperitoneal fluid with echogenic particles, single or multiple pseudocysts, hepatic or splenic calcifications, and collapsed bowel loops or obstruction.[14] There are four typical presentations of complicated meconium ileus including meconium pseudocyst with a calcified fibrous wall and bowel loops peripheral and usually posterior to the cyst, dense vascular adhesions with scattered calcifications, meconium ascites, and infected meconium ascites.[26,29] Again, creation of an ostomy is usually necessary to relieve the obstruction and for ongoing irrigation postoperatively. In some of these cases such as meconium cyst, the bowel may be very difficult to find and may be hidden posterior to the cyst rind. To find the bowel, it is necessary to make the abdominal incision laterally and attempt to get behind the cyst rind from the side. Because the bowel may be difficult to discern, an ostomy is usually the best option with later reoperation for establishing intestinal continuity once the inflammation has resolved.

Postoperative Care and Outcomes

Postoperative management includes ongoing fluid resuscitation with ostomy closure as soon as feasible.[13] Once the bowel has been cleared of meconium, oral feeds with pancreatic enzyme supplementation may be initiated. An evaluation of a cystic fibrosis database from 1990 to 2010 identified 75 neonates with meconium ileus of which 92% underwent laparotomy and 72% received ostomies.[30] In this series as well as in others, those who required an ostomy or had complicated meconium ileus had a longer length of stay.[30]

Long-term Complications (Distal Intestinal Obstruction Syndrome, Fibrosing Colonopathy, Rectal Prolapse)

Distal Intestinal Obstruction Syndrome

Previously referred to as meconium ileus equivalent, distal intestinal obstruction syndrome (DIOS) has two presentations: complete and incomplete. Incomplete DIOS, also known as impending DIOS, is defined as intestinal obstruction accompanied by a fecal mass in the ileo-cecum and abdominal pain or distension. Complete DIOS includes all of the previous symptoms with the addition of bilious emesis or air–fluid levels on abdominal radiograph.[31] DIOS is more prevalent in adults than children with cystic fibrosis and has an estimated prevalence of 15 to 20% of patients with cystic fibrosis.[23,32–34] Nearly 50% of patients with DIOS have a history of meconium ileus.[23,34]

The etiology of DIOS is thought to be related to a delayed transit of thickened secretions in the lumen of the gastrointestinal tract.[12] It has been proposed that pancreatic insufficiency leads to high fecal fat, which increases stool viscosity and activates the ileal break, delaying transit of intraluminal contents.[23] The ileal break is a feedback loop that is activated by fat in the ileum and slows jejunal motility, delays gastric emptying, and reduces small intestinal transit of solid and liquid intraluminal contents.[35] This hypothesis has been contradicted by the observation of DIOS in patients with cystic fibrosis without exocrine pancreatic dysfuntion.[36] In the terminal ileum, bile salts normally trigger increased secretion with a mechanism that is dependent on CFTR. A defect in CFTR causes decreased bile acid-stimulated secretion in the terminal ileum, which has been proposed as a part of the mechanism for DIOS. Malfunction of CFTR also causes increased sodium and water reabsorption through the epithelial sodium channels (ENaCs) in the terminal ileum.[36] Distinct from constipation ,which consists of diffuse stool impaction in the colon, DIOS is characterized by fecal material causing obstruction at the terminal ileum and in the small bowel.[36] Risk factors for DIOS include a previous history of meconium ileus, pancreatic insufficiency, genotype associated with a severe phenotype, previous history of DIOS, fat malabsorption, dehydration, and transplantation.[36–39]

Treatment of DIOS is primarily medical. If the obstruction is incomplete, the patient should receive oral rehydration, stool softeners, and laxatives such as polyethylene glycol.[36] If the obstruction is complete without bilious emesis, the patient may be rehydrated and given polyethylene glycol. If the patient presents with complete obstruction and severe bilious emesis, hospitalization with intravenous fluid, nasogastric decompression, and Gastrografin enemas are required.[31,36] Operative intervention is seldom required with aggressive medical management. However, if the patient fails medical management, celiotomy with enterotomy and possible resection may be necessary.[36,37]

Rectal Prolapse

Cystic fibrosis only accounts for approximately 11% of rectal prolapse in pediatric patients; however, 23% of patients with cystic fibrosis will be diagnosed with rectal prolapse.[40,41] Prior to widespread newborn screening, rectal prolapse preceded the diagnosis of cystic fibrosis in more than 40% of cases.[42] Since rectal prolapse may be a presenting symptom of undiagnosed cystic fibrosis, testing should be performed in all pediatric patients who present with this finding.[23,40,41] Rectal prolapse has a similar incidence in male and female patients with cystic fibrosis.[23,40,42] Among patients with cystic fibrosis, those presenting with rectal prolapse have a young average age at diagnosis ranging from 1 to 2.5 years in one series[42] and 3.7 years in another.[26] It has been proposed that the higher incidence of rectal prolapse in children younger than 4 years is related to anatomical factors such as the straight course of the rectum, low position of the rectum relative to other pelvic organs, mobility of the sigmoid colon, and weakness of the levator ani muscle.[40] In addition, there is only a loose attachment of the mucosa to the underlying muscularis and absence of Houston's valves in 75% of children under 1 year of age.[40] Many of these anatomic factors resolve in early childhood, diminishing the possibility of rectal prolapse. The proposed etiology of rectal prolapse among patients with cystic fibrosis is the presence of large voluminous stool and malnutrition in combination with increased intra-abdominal pressure from

chronic coughing.[40] It was also noted by Stern et al that of the 29 patients diagnosed with cystic fibrosis who had recurrent rectal prolapse, the problem resolved completely in 72% of patients after pancreatic enzyme supplementation was initiated.[42] In contrast, if patients were already taking supplemental enzymes prior to presentation with rectal prolapse, manipulation of the dosages had a little effect on the rectal prolapse.[42]

Typical management of rectal prolapse in children with cystic fibrosis includes manual reduction, which is successful in almost all cases. Occasionally, a patient may experience multiple episodes that are either painful or intolerable.[42] In these cases, sclerotherapy, a subcutaneous perianal suture or a sling procedure may be necessary.[40,42] Injection of a sclerosing agent into the rectal submucosa has success rates as high as 90 to 100%.[40] A variety of surgical methods have been proposed and the favored technique appears to be institution dependent, and is discussed in greater detail in this edition in the chapter on "rectal prolapse."

Fibrosing Colonopathy

Fibrosing colonopathy is a complication of cystic fibrosis that was first reported in 1994 by Smyth et al and is characterized by concentric rings of fibrosis deep to the submucosa, most frequently in the ascending colon, though it may involve the entire colon. It also involves hypertrophy of the muscularis mucosa as well as inflammation and fibrosis of the submucosa.[23,43] The etiology of fibrosing colonopathy was originally thought to be associated with high dosages of enzyme supplementation. This is according to a 1997 study that found a relative risk of fibrosing colonopathy that was double for those on high enzyme doses.[44–48] However, the occurrence of this complication appears to be multifactorial, as there have been cases documented in patients who had never received pancreatic enzyme supplementation.[49] It has been hypothesized that increased IgG in response to pancreatic enzymes occurred after ingestion, with a peak elevation at 7 to 9 months following initiation. This timing coincided with the development of fibrosing colonopathy.[50] Treatment of fibrosing colonopathy in general includes subtotal versus total colectomy depending on the extent of disease.[23,26,51] Ostomy may be necessary for rectal strictures though pull-through operations have been described.[29] There are small case reports of using steroids that have allowed strictures to resolve.[51]

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